**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 501/34, A61K 31/425

A1

(11) International Publication Number: **WO 98/43980**

(43) International Publication Date: 8 October 1998 (08.10.98)

(21) International Application Number: PCT/KR97/00194

(22) International Filing Date: 14 October 1997 (14.10.97)

(30) Priority Data:
1997/11765 31 March 1997 (31.03.97) KR

(71) Applicants *(for all designated States except US)*: DAE-WOONG PHARMACEUTICAL CO., LTD. [KR/KR]; 223-23, Sangdaewon-dong, Joongwon-ku, Sungnam, Kyunggi-do 462-120 (KR). DAE WOONG CHEMICAL CO., LTD. [KR/KR]; 906-5, Sangsin-ri, Hyangnam-myum, Hwasung-gun, Kyunggi-do 445-920 (KR).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: YOON, Geal, Jung [KR/KR]; Ilsung Apt. 1502, Sangdaewon-1dong, Joongwon-ku, Sungnam, Kyunggi-do 462-121 (KR). JEONG, Hee, Sun [KR/KR]; 618-118, Anyang-5dong, Manan-ku, Anyang, Kyunggi-do 430-015 (KR). YIM, Seong, Soo [KR/KR]; 277, Sangdaewon-3dong, Joongwon-ku, Sungnam, Kyunggi-do 462-123 (KR).

(74) Agent: HUH, Sang, Hoon; 13th floor, Hyecheon Building, 831, Yeoksam-dong, Kangnam-ku, Seoul 135-792 (KR).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*

(54) **Title:** A PROCESS FOR PREPARING AN AMORPHOUS CEFUROXIME AXETIL HAVING A LOW MELTING POINT

(57) **Abstract**

This invention relates to a process for preparing an amorphous cefuroxime axetil having a low melting point, more particularly, in which a solid medium including cefuroxime axetil homogeneously is prepared and wherein water is added at lower temperature than the melting point of the solid medium to gain an amorphous cefuroxime axetil having low melting point and high bioavailability in high purity and in high yield.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | | | TR | Turkey |
| BG | Bulgaria | HU | Hungary | ML | Mali | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MN | Mongolia | UA | Ukraine |
| BR | Brazil | IL | Israel | MR | Mauritania | UG | Uganda |
| BY | Belarus | IS | Iceland | MW | Malawi | US | United States of America |
| CA | Canada | IT | Italy | MX | Mexico | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NE | Niger | VN | Viet Nam |
| CG | Congo | KE | Kenya | NL | Netherlands | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NO | Norway | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | NZ | New Zealand | | |
| CM | Cameroon | | | PL | Poland | | |
| CN | China | KR | Republic of Korea | PT | Portugal | | |
| CU | Cuba | KZ | Kazakstan | RO | Romania | | |
| CZ | Czech Republic | LC | Saint Lucia | RU | Russian Federation | | |
| DE | Germany | LI | Liechtenstein | SD | Sudan | | |
| DK | Denmark | LK | Sri Lanka | SE | Sweden | | |
| EE | Estonia | LR | Liberia | SG | Singapore | | |

# A PROCESS FOR PREPARING AN AMORPHOUS CEFUROXIME AXETIL HAVING A LOW MELTING POINT

## BACKGROUND OF THE INVENTION

This invention relates to a process for preparing an amorphous cefuroxime axetil having a low melting point, more particularly, in which a solid medium including cefuroxime axetil homogeneously is prepared and wherein water is added at lower temperature than the melting point of the solid medium to give an amorphous cefuroxime axetil having low melting point and high bioavailability in high purity and in high yield.

### Description of the Prior Art

"An amorphous cefuroxime axetil having a low melting point" means that an amorphous cefuroxime axetil has the melting point of 94 ~ 96℃ and belongs in $A^{I}$ between amorphous $A^{I}$ and amorphous $A^{II}$ designated on Acta Polon. Pharm.-Drug research Vol. 52, No 5, pp 397 ~ 401, 1995.

Cefuroxime is a valuable antibiotics which has a broad spectrum activity against gram-positive and gram-negative microorganisms and is used widely in clinical practice since it's well tolerated in the mammalian body. However, when cefuroxime is administered orally, it is poorly absorbed in the gastro-intestinal tract and exist in sera and urine in low concentration, and hence cefuroxime is administered not orally but paranterally. Therefore, there has been a need for new cefuroxime preparation which can be easily absorbed in the gastro-intestinal tract following oral administration.

It is very important for the oral-administration of the cephalosporin compounds, including cefuroxime, to maximize the absorption of antibiotic in the gastro-intestinal tract and to minimize the amount of antibiotic-remaining

in it, hence resulting in high bioavailability. The antibiotic which is not absorbed will be ineffective for its clinical use and may cause side-effects in the gastro-intestinal tract. Meanwhile, when carboxyl group of cefuroxime is esterified appropriately, the absorability of the cefuroxime in the gastro-intestinal tract is increased remarkably and the esterfying group is hydrolysed by enzymes existing in serum and body tissues to give the antibiotically active parent acid. Cefuroxime axetil is one of the most important compound among the esterified cefuroxime compounds. Cefuroxime axetil is named as 1-acetoxyethyl (6R,7R)-3-carbamoyloxymethyl-7-[(Z)-2-(pur-2-yl)-2-(methoxyimino)acetamido]cef-3-m-4-carboxylate (syn isomer) and is useful for the treatment of a variety of diseases or infections caused by pathogenic bacteria through oral or rectal administration.

It was reported by British Patent No. 1,571,683 that cefuroxime axetil is produced in either crystal or amorphous form.

In addition, cefuroxime axetil different from previous cephalosporin compounds in its character has better bioavailability and chemical stability in amorphous form than those in crystal form. The process for preparing an amorphous cefuroxime axetil was applied for patents(European Patent No. 107,276, Korean Patent No. 42,097)

Cefuroxime axetil possesses an asymmetric carbon atom at the 1 position of 1-acetoxyethyl group and the compound can hence exist in the form of R- or S-isomer or mixtures of them. In the case of amorphous cefuroxime acetil, the mixture of R- and S-isomers has a higher bioavailability and an improved solubility than amorphous R-isomer or S-isomer alone. In mixing ratio of R-isomer and S-isomer, the molar ratio of R-isomer to S-isomer may be ranged 0.9:1 to 1.1:1, preferably 1:1(European Patent No. 107,276, Korean Patent No. 42,097).

In addtion, amorphous cefuroxime axetil is differ in physical and chemical characteristics depending on the preparation process(Acta Poloniac Pharmaceutica-Drug Research, Vol. 52, No. 5, pp397 ~ 401, 1995). An amorphous cefuroxime axetil has the m.p. of 94 ~ 96℃ when it is prepared by rapid solvent evaporation method but it has the m.p. of 135 ~ 138℃ when prepared by solvent precipitation method which precipitates the cefuroxime axetil by adding cefuroxime axetil solution into stirring another polar solvent. The difference such as the m.p. causes the change of physical properties, and then its change causes difference in its bioavailability. Consequently, the amorphous cefuroxime axetil having a melting point of 94 ~ 96℃ shows the most superior bioavailability.

There are several prior art such as spray drying, roller drying, solvent precipitation and lyophilization.(European Patent No. 107,276, Korean Patent No. 42,097). First, spray-drying, which removes solvent through rapid solvent evaporation after spraying solution, is the most desirable method for the preparation of amorphous cefuroxime axetil among the patented methods. However, spray-drying method has many disadvantages in its use. That is, it needs complicated installation of equipment and cannot remove the impurities included in either starting material or formed newly in the process and may possess some crystal form with substantial amounts of amorphous cefuroxime axetil depending on its condition of the process. Also, the yield is low or not constant as varied between 50.6 and 90%.

Secondly, roller-drying is the method which evaporizes the solvent rapidly from solution at the surface of roller and has the similar disadvantages as spray-drying. In addition, it needs complicated facilities and manipulation and cannot remove impurities included in either starting material or newly formed. It is very inconvenient to be industrialization

because the product should be taken out from roller.

Spray drying and roller drying are the rapid evaporation methods that remove the solvent from solution by evaporizing the solvent rapidly.

Thirdly, solvent precipitaion is the method that precipitates the product by mixing solution with different polarity of solvents and it has following disadvatages. It can include crystal form with substantial amounts of amorphous form depending on its condition of preparation and its yield is low or not constant as 68.3 to 91.7%. Moreover, the solution should be added slowly in the process of precipitation to protect from coagulation, and it needs sensitive processes such as blowing gas continuously or mixing with various solvents.

Finally, lyophilization is the method which produces the product through sublimation of the solid which includes the cefuroxime axetil homogeneously at a temperature lower than the m.p. of solid. It has many disadvantages as follows. This method needs expensive and complicated facilities and can not remove the impurities included in starting material. And it needs extra purification process in which the products are broken into small pieces and sieved and dried again after lyophilizing for appropriate hours because it's very difficult to remove the solvent completely by this method.

## SUMMARY OF THE INVENTION

We, inventors, have long been associated with the research for the easy preparation of amorphous cefuroxime axetil having a low m.p. and a high bioavailability. From our research we have established the method for preparing easily amorphous cefuroxime axetil of $A^1$ type having a low m.p. as follows. The solid including the cefuroxime axetil homogeneously is

prepared and water is added into the solid at a temperature lower than m.p. of the solid medium and stirred to afford amorphous cefuroxime axetil precipitate, which was filtered, washed and dried at reduced pressure to give the desired product.

Therefore, the object of this invention is to provide the process of preparing amorphous cefuroxime axetil having a low m.p., a high purity and also high bioavailability.

This invention relates to a process for preparing the amorphous cefuroxime axetil having a low melting point, characterized by comprising the following steps of

(a) Step for preparing the fused solution including cefuroxime axetil homogeneously by adding crystal cefuroxime axetil alone or the mixture of crystal and amorphous cefuroxime axetil to a melted solid medium maintained at higher temperature than the melting point of itself;

(b) Step for preparing a solid including cefuroxime axetil homogeneously by cooling the said fused solution to lower temperature than a m.p.;

(c) Step for preparing a precipitate of amorphous cefuroxime axetil having a low melting point by adding water at lower temperature than a melting point of the solid medium into the said solid; and

(d) Step for recovering the said precipitate.

## DETAILED DESCRIPTION OF THE INVENTION

This invention relates to preparing amorphous cefuroxime axetil having a low m.p. and high bioavailability from crystal cefuroxime axetil alone or the mixture of crystal and amorphous cefuroxime axetil.

First, after the fused solution is prepared from the solid medium by keeping a higher temperature than the m.p. of the solid medium, crystal cefuroxime or the mixture of crystal and amorphous cefuroxime axetil are dissolved in the solution. At this time, it is desirable to choose the solid medium which has relatively high m.p. at between 0 and 25℃ and can mix with water. If the m.p. of the solid medium is lower than 0℃, coagulation may be occurred when water is added at lower temperature than the m.p. of the solid medium. If the m.p. of the solid medium is higher than 25℃, it's inconvenient because the solid should be heated to be dissolved and then can be used.

A medium material of liquid phase which can be used for the solid medium in this invention may be dimethylsulfoxide, dioxane or t-butylalcohol, preferably dimethylsulfoxide or dioxane.

The solid medium including the cefuroxime axetil homogeneously is obtained by cooling the used medium material to lower temperature than the m.p. of the solid medium. At this time, if the cooling temperature is kept higher than the m.p. of the solid medium, the medium material in liquid phase is mixed with water rapidly to give the rapid precipitation of cefuroxime axetil resulting in coagulation and it is difficult to recover the precipitate in the next process in which water is added.

It is desirable to cool the solid medium to lower temperature than the m.p. of the solid medium by a temperature differenc of 5℃ to 25℃. When the medium is cooled at lower temperature than the m.p. of the medium by a temperature difference of less than 5℃, a small amount of the solid medium can be mixed together in liquified state and coagulation can be occurred due to the excellerated solubility of the solid medium when precipitate is trying to be obtained by adding water. In addition, when the solid medium is cooled

at lower temperature than the m.p. of the medium by a temperature difference more than 25℃, precipitate is possibly not formed because the solid medium is not solubilized smoothly. This is because that, when water is added in the next process, water is frozen at the surface of the solid medium being contacted. It is not economical because it's expensive to keep a low cooling temperature.

In the following process is a precipitate formed by adding water into a solid medium kept a cooling temperature of the above and following by stirring. It is desirable at this time to keep water being added to the solid medium at lower temperature than the m.p. of it. If water being added is kept at higher temperature than the m.p. of the solid medium, some coagulation can be occurred by being-increased of the solubility of the solid medium into water. Adding water maintained at a temperature between 0℃ and 5℃ is most desirable. It is convenient and hence advantageous to use water of a temperature between 0 and 5℃ because it can be prepared easily by adding water to ice without special adjustment of temperature.

In the process of precipitate-forming, it is desirable to add water 15 ~ 20 times by volume as much as solid medium used and to stir with a speed of 600 ~ 1000 rpm for 10 to 30 minutes.

The precipitate formed is filtered at reduced pressure and sequentially washed with water and hexane, and dried under vaccum for about 20 hours at 40 ~ 60℃.

Through the preparing process described as the above, amorphous cefuroxime axetil having a low m.p. is obtained reproducibly in higher than 95% yield. According to the result analysed by HPLC, amorphous cefuroxime axetil having a low m.p. obtained by the process of this invention is the absolutely pure product having its purity higher than 97%, and the mole

ratio of R-isomer to S-isomer is 1:0.9 to 1:11 and is shown as desirable. In addition, amorphous cefuroxime axetil of this invention has a m.p. of 94 ~ 96℃ as a range showing a best bioavailability.

This invention of new process which is completely different from the prior art, has the advantages of producing an exclusively amorphous cefuroxime axetil in high yield through easy and simple manipulation.

As shown in the above, this invention is completely different from the prior art in that the product is obtained by dissolving it in water with keeping the solid medium in solid state at lower temperature than its m.p.. The prior art as the above-mentioned includes roller-drying and spray drying method which give the procuct by removing the solvent rapidly after evaporation of solvent, and solvent precipitate method which produces the product by mixing the solution with another different polarity of solvent.

The freezing precipitation according to this invention is completely new method in principle which has never been introduced in any method before. In addition to this, this invention doesn't require special equipments or facilities, and uses a cheap water as a main solvent, whilst rapid solvent removing techinque for the rapid removal of solvent needs special equipment, and lyophilization method needs special equipment for keeping the reduced pressure for the sublimation of solvent, too. And this invention also has advantage of providing exclusively amorphous cefuroxime axetil having a low m.p. in high purity and in high yield as well as a high bioavailability, whilst solvent precipitate can produce the amorphous cefuroxime axetil having a high m.p. or small amounts of crystal form.

This invention is described in more detail by the following examples, but the claim is not limited to these examples.

In addition, the crystal cefuroxime axetil used in the following

examples was prepared in high purity by following the procedure of the Brithish Patent No. 1,571,683.

EXAMPLE 1

Crystal cefuroxime axetil (2g, mixture of R- and S-isomer) was dissolved in dimethylsulfoxide(7 mL) and cooled to 0℃ to freeze. Water(110 mL) at 5℃ was added and stirred for 15 minutes. The resulting precipitate was separated by filteration and washed sequentially with $H_2O$(50 mL), cyclohexane, then dried for 20 hours at 50℃ under vacuum to produce 1.9 g of amorphous cefuroxime axetil.

Yield: 95%

HPLC analysis:

Amorphous cefuroxime Axetil: 97.4%

Ceph-2-em compound: 0.2%

Impurities: 1.2%

R-isomer/S-isomer ratio(HPLC): 1.02/1

Water content(Karl Filscher): 1.0%

m.p.: 94 ~ 96℃

NMR(DMSO-$d_6$, ppm): $\delta$ 1.5(d, 3H), 2.0(d, 3H), 3.4 ~ 3.6(m, 2H), 3.9(s, 3H), 4.5 ~ 4.8(m, 2H), 5.2(m, 1H), 5.8(m, 1H), 6.5 ~ 6.7(m, 4H), 6.8 ~ 7.0(m, 1H), 7.8(m, 1H), 9.7(d, 1H)

IR(KBr, $cm^{-1}$): 3480 or 3210(NH, $NH_2$ complex), 1782($\beta$-lactam), 1760(acetate), 1720(4-ester group), 1720 and 1594(carbamate), 1676 and 1534(7-amido)

XRD(Shimadzu DX-1 power diffractometer): The sample was mounted at sample holder and diffraction peak was obtained at the speed 4 ° /min with 30kv, 30mA of Cuka line. At this time, the peaks were shown halo which is

typical for the amorphous form. And hence the product was identified as an amorphous form with no crystal form.

EXAMPLE 2.

Crystal cefuroxime axetil (100g, mixture of R- and S-isomer) was dissolved in dimethylsulfoxide(350 mL) and cooled to 0℃ to freeze. Water(5.3 L) of 5℃ was added and stirred for 20 minutes. The resulting precipitate was separated by filteration and washed sequentially with $H_2O$(2.5 L) and cyclohexane, then dried for 20 hours at 50℃ under vacuum to produce 95.6 g of amorphous cefuroxime axetil.

Yield: 95.6%

HPLC analysis:

Amorphous cefuroxime Axetil: 97.0%

Ceph-2-em compound: 0.3%

Impurities: 1.3%

R isomer/S isomer ratio(HPLC): 1.04/1

Water content(Kari Filscher): 1.1%

m.p.: 94 ~ 96℃

NMR(DMSO-$d_6$, ppm): $\delta$ 1.5(d, 3H), 2.0(d, 3H), 3.4 ~ 3.6(m, 2H), 3.9(s, 3H), 4.5 ~ 4.8(m, 2H), 5.2(m, 1H), 5.8(m, 1H), 6.5 ~ 6.7(m, 4H), 6.8 ~ 7.0(m, 1H), 7.8(m, 1H), 9.7(d, 1H)

IR(KBr, $cm^{-1}$): 3480 or 3210(NH, $NH_2$ complex), 1782($\beta$-lactam), 1760(acetate), 1720(4-ester group), 1720 and 1594(carbamate), 1676 and 1534(7-amido)

XRD(Shimadzu DX-1 power diffractometer): The sample was mounted at sample holder and differaction peak was obtained at the speed 4 ° /min with 30kv, 30mA of Cuka line. At this time, the peaks were shown halo which is

typical for the amorphous form. And hence the product was identified as an amorphous form with no crystal form.

EXAMPLE 3

Crystal cefuroxime axetil (2g, mixture of R and S isomer) was dissolved in dioxane(6 mL) and cooled to 0℃ to freeze. Water(100 mL) at 5℃ was added and stirred for 15 minutes. The resulting precipitate was separated by filteration and washed sequentially with $H_2O$(50 mL) and cyclohexane, then dried for 20 hours at 50℃ under vacuum to produce 1.9 g of amorphous cefuroxime axetil.

Yield: 95.0%

HPLC analysis:

Amorphous cefuroxime Axetil: 96.8%

Ceph-2-em compound: 0.3%

Impurities: 1.4%

R isomer/S isomer ratio(HPLC): 0.98/1

Water content(Karl Filscher): 1.1%

m.p.: 95 ~ 97℃

NMR(DMSO-$d_6$, ppm): $\delta$ 1.5(d, 3H), 2.0(d, 3H), 3.4 ~ 3.6(m, 2H), 3.9(s, 3H), 4.5 ~ 4.8(m, 2H), 5.2(m, 1H), 5.8(m, 1H), 6.5 ~ 6.7(m, 4H), 6.8 ~ 7.0(m, 1H), 7.8(m, 1H), 9.7(d, 1H)

IR(KBr, $cm^{-1}$): 3480 or 3210(NH, $NH_2$ complex), 1782($\beta$-lactam), 1760(acetate), 1720(4-ester group), 1720 and 1594(carbamate), 1676 and 1534(7-amido)

XRD(Shimadzu DX-1 power diffractometer): The sample was mounted at sample holder and diffraction peak was obtained at the speed of 4 °/min with 30kv, 30mA of Cuka line. At this time, the peaks were shown halo

which is typical for the amorphous form. And hence the product was identified as an amorphous form with no crystal form.

As mentioned in the above, the process according to this invention doesn't need special equipments for the rapid evaporation of solvent or for keeping the vacuum state to remove the solid medium by sublimation. Water is used as a cheap solvent and it is especially useful for industrialization since it's possible to produce amorphous cefuroxime axetil having a low m.p., high purity, and high yield as well as a high bioavailability.

## CLAIMS

What is claimed is:

1. A process for preparing amorphous($A^I$) cefuroxime axetil having a low melting point, characterized by comprising the following steps of

(a) Step for preparing the fused solution including cefuroxime axetil homogeneously by adding crystal cefuroxime axetil alone or the mixture of crystal and amorphous cefuroxime axetil to a melted solid medium maintained at higher temperature than the melting point of itself;

(b) Step for preparing a solid including cefuroxime axetil homogeneously by cooling the said fused solution to lower temperature than a m.p.;

(c) Step for preparing a precipitate of amorphous cefuroxime axetil having a low melting point by adding water at lower temperature than a melting point of the solid medium into the said solid; and

(d) Step for recovering the said precipitate.

2. The process according to claim 1, wherein the solid medium in said step (a) has a melting point between 0 and 25℃.

3. The process according to claim 2, wherein the solid medium in said step (a) is selected from the group consisting of dimethylsulfoxide, dioxane and t-butanol.

4. The process according to claim 1, wherein the cooling temperature of the solid medium in said step (b) is lower than the melting point of the solid medium by the temperature difference of 5℃ to 25℃.

5. The process according to claim 1, wherein the water in said step (c) is at a temperature between 0℃ and 5℃.

5

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 97/00194

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 D 501/34; A 61 K 31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 D 501/34

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | DE 33 27 449 A1 (GLAXO GROUP LTD.) 02 February 1984 (02.02.84), abstract. | 1-5 |
| A | DE 39 14 658 A1 (GLAXO GROUP LTD.) 16 November 1989 (16.11.89), claims 1-11. | 1-5 |
| A | GB 2 218 091 A (GLAXO GROUP LTD.) 08 November 1989 (08.11.89), abstract. | 1-5 |
| A | US 5 063 224 A (MOSHER et al.) 05 November 1991 (05.11.91), claims 1-6. | 1-5 |

---

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 18 December 1997 (18.12.97) | 05 January 1998 (05.01.98) |

| Name and mailing address of the ISA/AT | Authorized officer |
|---|---|
| AUSTRIAN PATENT OFFICE<br>Kohlmarkt 8-10<br>A-1014 Vienna | Brus |
| Facsimile No. 1/53424/535 | Telephone No. 1/53424/519 |

Form PCT/ISA/210 (second sheet) (July 1992)

DE3327449

Process for preparing cefuroxime axetil. There is described a product which is a highly pure substantially amorphous form of cefuroxime axetil (cefuroxime 1-acetoxyethyl ester) which is stable, which has increased absorption via the gastro-intestinal tract and has a correspondingly high level of bioavailability on oral or rectal administration. Methods of preparing the product are also described which involve the recovery of the product from a solution thereof. A preferred method is the use of spray drying techniques, though roller drying, solvent precipitation or freeze-drying are also described. Also disclosed are pharmaceutical compositions containing the product and methods for its use in medicine.

DE 3914658

Preparation of cefuroxime axetil and analogs were prepared by carbamoylation of formula (I) (R1 = H) followed by optional further conversion. Thus, K(6R,7R)-7-[(Z)-2-(2-furyl)-2-methoxyiminoacetamido]-3-hydroxymethylceph-3-em-4-carboxylate was stirred 45 min at –10 to 0° in DMF with BrCHMeOAc followed by addition of $ClSO_2NCO$ and 30 minutes stirring at =° to give, after hydrolysis, cefuroxime axetil.

GB 2218091

This invention relates to improvement in or relating to cephalosporins. More particularly it relates to processes for the preparation of the oral antibiotic cefuroxime axetil. The inventors now have devised a process for the preparation of cefuroxime axetil and derivatives thereof in which the methyl group in the 7-oxime substituent is introduced as the last major chemical step in the synthesis by a methylation reaction. The methylation agent may be, for example, an organic halide or sulphate, or a sulphonate such as tosylate, and may thus be a methyl halide (e.g. methyl iodide) or dimethylsulphate.

US 5063224

R-Cefuroxime axetil which is substantially free of the S-isomer is readily absorbed from the stomach and gastro-intestinal track of animals, and is therefor ideally suited to oral therapy of bacterial infections. Such selective administration results in surprisingly greater biovailability of cefuroxime, and thus dramatically reduces the amount of unabsorbable cefuroxime remaining in the gut lumen, thereby diminishing adverse side effects attributable to cefuroxime.

**INTERNATIONAL SEARCH REPORT**
Information on patent family members

International application No.
PCT/KR 97/00194

| In Recherchenbericht angeführtes Patentdokument *Patent document cited in search report Document de brevet cité dans le rapport de recherche | Datum der Veröffentlichung Publication date Date de publication | Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets | Datum der Veröffentlichung Publication date Date de publication |
|---|---|---|---|
| DE A1 3327449 | 02-02-84 | AT A 2767/83 | 15-06-86 |
| | | AT B 382154 | 26-01-87 |
| | | AU A1 17417/83 | 02-02-84 |
| | | AU B2 566881 | 05-11-87 |
| | | BE A1 897422 | 30-01-84 |
| | | CA A1 1240313 | 09-08-88 |
| | | CH A 657134 | 15-08-86 |
| | | CS A2 8305687 | 15-03-88 |
| | | CS B2 259515 | 14-10-88 |
| | | CY A 1434 | 02-09-88 |
| | | CZ A3 9104031 | 12-05-93 |
| | | CZ B6 280528 | 14-02-96 |
| | | DE C0 3374010 | 12-11-87 |
| | | DK A0 3490/83 | 25-07-83 |
| | | DK A 3490/83 | 31-01-84 |
| | | DK A 683/92 | 25-05-92 |
| | | DK A0 683/92 | 25-05-92 |
| | | DK B 164507 | 06-07-92 |
| | | DK C 164507 | 23-11-92 |
| | | EP A2 107276 | 02-05-84 |
| | | EP A3 107276 | 06-03-85 |
| | | EP B1 107276 | 07-10-87 |
| | | ES A1 8505590 | 01-06-85 |
| | | ES A5 8524590 | 28-06-85 |
| | | ES A1 8505689 | 01-10-85 |
| | | FI A0 832757 | 29-07-83 |
| | | FI A 832757 | 31-01-84 |
| | | FI B 76093 | 31-05-88 |
| | | FI C 76093 | 09-09-88 |
| | | FR A1 2531087 | 03-02-84 |
| | | FR B1 2531087 | 22-11-85 |
| | | GB A0 8320518 | 01-09-83 |
| | | GB A1 2127401 | 11-04-84 |
| | | GB B2 2127401 | 16-04-86 |
| | | GR A 79349 | 22-10-84 |
| | | HK A 842788 | 28-10-88 |
| | | HU B 190603 | 28-09-86 |
| | | IE B 55748 | 02-01-91 |
| | | IL A0 69375 | 30-11-83 |
| | | IL A1 69375 | 31-12-86 |
| | | IT A0 8348789 | 29-07-83 |
| | | IT A 1168206 | 20-05-87 |
| | | JP A2 59044391 | 12-03-84 |
| | | JP B4 7030084 | 05-04-95 |
| | | KE A 3805 | 03-06-88 |
| | | KR B1 9100046 | 19-01-91 |
| | | LU A 84935 | 23-11-83 |
| | | MY A 58/87 | 31-12-87 |
| | | NL A 8302705 | 16-02-84 |
| | | NO A 832777 | 31-01-84 |
| | | NO B 163897 | 30-04-90 |
| | | NO C 163897 | 08-08-90 |
| | | NZ A 205083 | 14-03-86 |
| | | PL A1 243228 | 27-08-84 |
| | | PL B1 156001 | 31-01-92 |
| | | PT A 77135 | 01-08-83 |
| | | PT B 77135 | 24-01-86 |
| | | SE A0 8304208 | 29-07-83 |
| | | SE A 8304208 | 31-01-84 |
| | | SE B 453195 | 18-01-88 |
| | | SE C 453195 | 28-04-88 |
| | | SG A 260/88 | 15-07-88 |
| | | SI A8 8311558 | 31-12-95 |
| | | SK A3 4031/91 | 11-07-95 |
| | | SK B6 277896 | 11-07-95 |
| | | SU A3 1268471 | 23-10-86 |
| | | US A 4562181 | 31-12-85 |
| | | US A 4820833 | 11-04-89 |
| | | US A 4994567 | 19-02-91 |
| | | US A 5013837 | 07-05-91 |
| | | YU A 1558/83 | 30-04-86 |

*Form PCT/ISA/210 (patent family annex) (July 1992)*

**INTERNATIONAL SEARCH REPORT**
Information on patent family members

International application No.
PCT/KR 97/00194

| | | | | | |
|---|---|---|---|---|---|
| | | | YU | B | 44680 31-12-90 |
| | | | ZA | A | 8305579 26-09-84 |
| | | | ZW | A | 173/83 26-10-83 |
| DE A1 | 3914658 | 16-11-89 | CH | A | 678856 15-11-91 |
| | | | FR | A1 | 2631031 10-11-89 |
| | | | GB | A0 | 8810394 08-06-88 |
| | | | GB | A0 | 8909987 21-06-89 |
| | | | GB | A1 | 2218093 08-11-89 |
| | | | IT | A0 | 8947902 02-05-89 |
| | | | IT | A | 1235502 05-09-92 |
| | | | JP | A2 | 2056490 26-02-90 |
| | | | KR | B1 | 9701531 11-02-97 |
| | | | NL | A | 8901111 01-12-89 |
| GB A | 2218091 | | GB | A0 | 8810392 08-06-88 |
| | | | GB | A0 | 8909985 21-06-89 |
| | | | GB | A1 | 2218091 08-11-89 |
| US A | 5063224 | 05-11-91 | keine - none - rien | | |